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EVALUATION OF RISK FACTORS ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT IN CASES WITH CHRONIC KIDNEY DISEASE

KRONİK BÖBREK HASTALIĞI OLAN BİREYLERDE HAFİF BİLİŞSEL FONKSİYON BOZUKLUĞU İLE İLİŞKİLİ RİSK FAKTÖRLERİNİN DEĞERLENDİRİLMESİ

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Keywords: Chronic kidney disease, cognitive function, mild cognitive impairment, hyponatremia, montreal cognitive assessment, risk factors

Anahtar Sözcükler: Kronik böbrek hastalığı, bilişsel fonksiyon, hafif bilişsel fonksiyon bozukluğu, hiponatremi, montreal bilişsel değerlendirme ölçeği, risk faktörleri

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SUMMARY

Introduction: *Cognitive impairment (CI) is common in chronic kidney disease (CKD). The aim of this study is to evaluate the demographic and clinical risk factors associated with mild cognitive impairment (MCI) in non-dialysis dependent CKD stage 3-5 patients.*

Material and methods: *This study was designed as a single center cross-sectional study. 145 patients with non-dialysis dependent CKD stage 3-5 were included in the study. A serum sodium level of <135 mmol/L was defined as hyponatremia. The patients were divided into two groups according to their sodium levels, as hyponatremia and normonatremia. Montreal Cognitive Assessment (MoCA) scale was used to evaluate cognitive functions. A MoCA score of 21 was described as mild cognitive impairment (MCI).*

Results: *The mean age of patients was 58.7±13.2 years and 54.4% of patients were female, 26.8% were diabetic and 47.5% were hypertensive. 22.7% of the patients had hyponatremia and 53.7% had MCI. Mean MoCA scores of CKD patients and control group, respectively; were 21.7 ± 1.9 (13-28) and 27.2 ± 2.8 (19-30) (p=0.013). MoCA scores of hyponatremic and normonatremic patients, respectively; 19.6 ± 3.1, 23.4 ± 3.8, and the difference was statistically significant (p=0.03). The incidence of MCI was 72.7% in hyponatremic patients and 48.2% in normonatremic patients (p=0.04). Advanced age (OR:1.452, p=0.037), diabetes (OR:2.028, p=0.016), diastolic blood pressure (OR:1.336, p=0.028), low sodium level (OR:1.439, p=0.011), hemoglobin (OR:1.523, p=0.026) and eGFR (OR:1.198, p=0.041) were determined as independent risk factors for MCI.*

Conclusion: *MCI is common in patients with CKD. MCI evaluation should be part of nephrological care. Early diagnosis of MCI and treatment of modifiable risk factors may slow the progression to overt cognitive impairment.*

ÖZ

Giriş: *Kronik böbrek hastalığında (KBH) bilişsel fonksiyon bozukluğu sık görülür. Bu çalışmanın amacı diyalize bağımlı olmayan KBH evre 3-5 hastalarda hafif bilişsel fonksiyon bozukluğu (HBB) ile ilişkili demografik ve klinik risk faktörlerinin değerlendirilmesidir.*

Gereç ve Yöntem: *Bu çalışma tek merkezli kesitsel bir çalışma olarak tasarlandı. Çalışmaya diyalize bağımlı olmayan KBH evre 3-5 olan 145 hasta dahil edildi. Serum sodyum düzeyinin <135 mmol/L olması hiponatremi olarak tanımlandı. Hastalar sodyum düzeyine göre hiponatremik ve normonatremik olmak üzere iki gruba ayrıldı. Bilişsel fonksiyonların değerlendirilmesinde Montreal Bilişsel Değerlendirme (MOBİD) ölçeği kullanıldı. MOBİD skoru <21 olması hafif bilişsel bozukluk (HBB) olarak tanımlandı.*

Bulgular: *Hastaların yaş ortalaması 58,7±13,2 yıl, %54,4'ü kadındı, %26,8'i diyabetik ve % 47,5'i' hipertansifti. Hastaların % 22,7' sinde hiponatremi ve %53,7'inde HBB vardı. KBH hastalarının ve kontrol grubunun ortalama MOBİD skorları sırasıyla; 21,7 ± 1,9 (13-28) ve 27,2 ± 2,8 (19-30) (p=0.013) idi. Hiponatremik ve normonatremik hastaların MOBİD skorları sırasıyla; 19,6 ± 3,1, 23,4 ± 3,8, ve aradaki fark istatistiksel açıdan anlamlıydı (p=0.03). Hiponatremik hastalarda HBB sıklığı %72,7, normonatremik hastalarda ise % 48,2 saptandı (p=0.04). İleri yaş (OR:1.452, p=0.037), diyabet (OR:2.028, p=0.016), diyastolik kan basıncı (OR:1.336, p=0.028), düşük sodyum düzeyi (OR:1.439, p=0.011), hemoglobin (OR:1.523, p=0.026) ve tGFH (OR:1.198, p=0.041) düzeyleri HBB için bağımsız risk faktörü olarak belirlendi.*

Sonuç: *HBB, KBH olan hastalarda sık gözlenir. HBB değerlendirmesi nefrolojik bakımın bir parçası olmalıdır. HBB'nin erken tanısı ve değiştirilebilir risk faktörlerinin tedavisi aşikar bilişsel bozukluğa ilerleyişi yavaşlatabilir.*

INTRODUCTION

Chronic kidney disease (CKD) is characterized by frequently progressive and irreversible damage to the nephrons, and its incidence in our country was reported as 15.7% in the CREDIT study (1). Involvement of the central and peripheral nervous system in patients with CKD manifests itself in a clinical spectrum in which stroke, peripheral sensory and motor neuropathy, autonomic neuropathy, concentration disorder called uremic encephalopathy, insomnia, memory, learning, attention and many cognitive functions are affected. The frequency of cognitive impairment (CI) in patients with CKD is increased compared to healthy individuals of the same age and is seen at earlier ages. The etiology of cognitive impairment (CI) in patients with CKD is usually multifactorial. Often, the combination of many factors such as uremic toxins, increased cardiovascular and cerebrovascular diseases, diabetes, hypertension, dyslipidemia, malnutrition and inflammation, metabolic acidosis, anemia, oxidative stress, and multiple drug use cause CI (2,3). The frequency of CI in patients with predialysis CKD is 13-70%, and it increases up to 77% in hemodialysis patients (4,5). When the glomerular filtration rate (GFR) is <60 ml/min/1.73m2 (CKD-Stage 3), cognitive impairment becomes more evident (4,5).

Although many uremic signs and symptoms, metabolic disorders (metabolic acidosis, hyperphosphatemia, hyperkalemia, etc.), hypertension and anemia improve with renal replacement therapy, cognitive functions do not improve at the same level, and deterioration continues with increasing progress in the future. Mortality rates of CKD patients with CI are increased compared to patients with normal cognitive function. CI causes decreased quality of life, decreased adherence to diet and medication, increased need for care, increased and prolonged hospitalization rates, and ultimately inadequate medical care in patients with CKD (6). Due to the high frequency of coexistence of CKD and CI, the evaluation of cognitive functions from the early stages of CKD is an important step to reduce the morbidities associated with this condition.

CI is defined as a newly developed deficit in at least two areas of cognitive functioning, and there are many scales used in its assessment. The Montreal Cognitive Assessment (MoCA) scale detects mild cognitive impairment (MCI) with high sensitivity and specificity. It is reliable in distinguishing individuals with MCI from Alzheimer type dementia and healthy individuals (7,8). The MoCA scale has been used in the diagnosis of MCI since 2005, but studies using this scale have increased in recent years (9).

Hyponatremia is the most common electrolyte disorder in outpatients and hospitalized patients

(10). Hyponatremia are classified according to sodium level as mild (130-135 mmol/L), moderate (129-125 mmol/L) and severe (<125 mmol/L) hyponatremia. Signs and symptoms of hyponatremia depend on the rate and severity of hyponatremia (11). While chronic hyponatremias are often asymptomatic or show mild symptoms due to the adaptation of the brain to hypoosmolarity, severe neurological symptoms and death may occur in acute hyponatremias (<48 h) due to osmotic brain edema (11). The incidence of hyponatremia in patients with CKD is 15-30%, and it often has a chronic course (11). In patients with CKD, hyponatremia develops due to many factors such as volume overload, multiple drug use, heart failure, diuretic use, CKD stage, excessive water intake, severe salt restriction or salt-losing nephropathies (12).

Hyponatremia is associated with CI in peritoneal dialysis and hemodialysis patients (13,14). Evaluation of CI is not yet part of nephrological care in the predialysis period, but evaluation of cognitive functions and associated risk factors can reduce morbidity and mortality. The aim of this study is to evaluate the relationship between MCI evaluated using the MoCA scale and hyponatremia and other risk factors in patients with non-dialysis dependent CKD stage 3-5.

MATERIAL and METHOD

Study population

This study was designed as a single-center, cross-sectional study. In this study included 237 patients who were followed up in the Nephrology outpatient clinic for at least one year, were older than 18 years, had a glomerular filtration rate of ≤60 ml/min/1.73m2, and were non-dialysis dependent CKD stage 3-5. After applying the exclusion criteria, the data of 145 patients were evaluated. The study was carried out between June 1, 2021 and September 15, 2021 after ethics committee approval. CKD was divided into five stages using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)-glomerular filtration rate (GFR) formula. CKD stage-1 GFR≥90 ml/min/1.73m^2, stage-2 GFR: 60-89.9 ml/min/1.73m^2, stage-3 GFR: 30-59.9 ml/min/ 1.73m^2, stage- 4 GFR: 15-29.9 ml/min/1.73m^2 and stage-5 GFR was defined as <15 ml/min/ 1.73 m^2. Age, gender, body mass index (BMI), education status, smoking and alcohol use, presence of diabetes and hypertension, systolic and diastolic blood pressure and medications of the patients were recorded. American Diabetes Association criteria were used for the diagnosis of diabetes (15). Hypertension was defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) ≥140/90 mmHg and/or use of antihypertensive medication. BMI was calculated with the formula of body weight (kg)/height (meter x meter, m2) (kg/m2).

Previous cerebrovascular disease (hemorrhagic, ischemic stroke), parkinson, dementia, depression, schizophrenia, and other active psychiatric diseases, active alcohol use, acute kidney injury, acute or chronic liver disease, hyperthyroidism-hypothyroidism, hypopituitarism, adrenal insufficiency, heart failure (ejection fraction <40%), severe anemia (hemoglobin <8 g/dL), malignancy, rheumatological disease, kidney transplant, steroids and immunosuppressive drug use, acute infection and acute inflammatory disease, illiterate patients who did not accept to participate in the study were not included in the study. Twenty-five age- and gender-matched patients without any health problems were included as the control group. There was no significant change in the salt and water consumption of the patients in the last month. Volume status was evaluated by clinical examination. The sodium levels of the patients were corrected according to their serum glucose levels. Hyponatremia was defined as a serum sodium level <135 mmol/L (16). The patients were divided into two groups as hyponatremic (n=33) and normonatremic (n=112). In addition, patients were divided into two groups according to the MoCA score, as MCI (<21 points) and normal cognitive function (≥21).

Assessment of cognitive functions

MoCA scale was used to evaluate cognitive functions. This scale is a simple and fast scale developed by Nasreddine et al. to distinguish individuals with MCI from healthy individuals (9). Eight cognitive functions are assessed in individuals, including short-term memory, visuospatial abilities, executive function, attention, concentration, working memory,

language, and orientation (9). It can also be administered by a trained healthcare professional who is not a neurologist or psychiatrist (3). MoCA score ranges from 0-30, and low scores indicate poor cognitive function. The use of MoCA in Turkish patients has been validated and the cut-off score is 21 to distinguish healthy individuals from individuals with MCI and Alzheimer's disease (7). Turkish version of MoCA was used in this study (7). The MoCA scores was administered to the patients by the same researcher (F.Y).

Laboratory analysis

Venous blood samples were taken from all patients after 12 hours of fasting. All biochemical parameters were measured in the central biochemistry laboratory. Glucose, urea, creatinine, uric acid, sodium, potassium, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), triglyceride level, total protein, albumin, calcium, phosphorus, Parathor, bicarbonate, C-reactive protein, spot urinary proteinuria and complete blood count were measured at the frequencies recommended in the guidelines. Proteinuria was found by dividing the spot protein (mg/g) and spot creatinine (mg/g) values in the first urine sample in the morning. All biochemical parameters were measured with a Roche Cobas 8000 automatic analyzer (Roche Diagnostics, Shanghai, Ltd.).

Statistical Analysis

The results were evaluated using the SPSS program version 23 (Statistical Package for the Social Sciences, version 23.0, SPSS Inc, Chicago, Ill, USA). Categorical variables were presented as a percentage (%) and compared using the Pearson chi-square test. The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Normally distributed parameters were expressed as mean±SD, and non-normally distributed parameters were expressed as median and range (IQR). To compare the numerical variables between groups, Student's t test was used if the data showed normal distribution and Mann-Whitney U test was used if it did not show normal distribution. Spearman and Pearson correlation analyzes were performed for the correlation of MoCA score with clinical and laboratory parameters. Univariate and multivariate logistic regression analysis were performed to evaluate the independent relationship between MCI and clinical and laboratory parameters. The effects were measured with odds ratios and 95% confidence intervals based on logistic regression models. In statistical evaluations, the significance level was accepted as $p<0.05$.

Ethical Statement

The study protocol was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (26.5.2021/KAEK-339). The research protocol was carried out in accordance with the Declaration of Helsinki. Written consents were obtained from the individuals participating in the study.

RESULTS

A total of 145 patients were included in this study. The basic demographic characteristics and CKD etiologies of the patients are shown in Table 1. There were no significant difference between the age, gender distribution and BMI of the CKD and control groups ($p>0.05$). Mean MoCA scores of patients with CKD and control group, respectively; they were 21.7 ± 1.9 (13-28) and 27.2 ± 2.8 (19-30) ($p=0.013$).

MCI was detected in 53.7% of the patients and hyponatremia was found in 22.7% of the patients. The frequency of hyponatremia and MCI according to CKD stages is shown in fig.1. There was no significant difference in the frequency of hyponatremia between CKD stages ($p>0.05$). The frequency of MCI in CKD stage-5 was statistically significantly higher than in stage-3 ($p=0.04$), but there was no significant difference between CKD stage-4 ($p=0.23$). Mild hyponatremia was detected in 81.8%, moderate in 12.1%, and severe in 6.1%of hyponatremic patients. 15.1% of hyponatremic patients had acute hyponatremia and 84.9% had chronic hyponatremia. MoCA scores of hyponatremic and normonatremia groups were respectively: 19.6 ± 3.1 (13-24); 23.4 ± 3.8 (19-28); and $p=0.03$. The frequency of MCI were 72.7% (n=24 patients) in hyponatremic patients and 48.2% (n=54 patients) in normonatremic patients ($p=0.04$).

Table 1. General characteristics of study population.

Parameter	All patients (n=145)
Age (years)	58.7±13.2 (28-83)
Female (n, %)	79, 54.4%
Diabetes mellitus (n, %)	39, 26.8%
Hypertension (n, %)	69, 47.5%
Hyperlipidemia (n, %)	46, 31.7%
BMI (kg/m^2)	27.2 ± 3.0 (22.4-35.8)
Smoking (n, %)	44, 30.3%
Education	
Primary school (n, %)	84, 57.9%
High school (n, %)	43, 29.7%
University (n, %)	18, 12.4%
CKD etiology	
Diabetes mellitus	37, 25.5%
Hypertension	18, 12.4%
Glomerulonephritis	9, 6.2%
Urolithiasis	9, 6.2%
Chronic pyelonephritis	7, 4.8%
Urological causes	7, 4.5%
Polycystic kidney disease	6, 4.2%
Unknown	29, 20%
Other's	23, 15.9%
CKD Stage (n,%)	
Stage-3	76, 52.4%
Stage-4	43, 29.6%
Stage-5	26, 18%

Abbreviations: CKD: Chronic kidney disease, BMI: Body mass index

The mean age of hyponatremic patients was significantly higher than in normonatremic patients: (67.5 ± 12.8 years, 54.3 ± 10.8 years, and p=0.02, respectively). Gender distribution, BMI, smoking and alcohol use, frequency of ischemic heart disease and hyperlipidemia were similar in both groups (p>0.05), but the frequency of diabetes was higher in the hyponatremic group (p<0.05). The systolic and dystolic blood pressures of the hyponatremic group were higher than the normonatremic group (148.2 ± 33.4 mmHg, 138.6 ± 31.5 mmHg, p=0.02 and 92.5 ± 11.3 mmHg, 85.6 ± 12.2 mmHg, p=0.03 respectively). The number of patients using diuretics (angiotensin converting enzyme inhibitors (ACEi)/Angiotensin-1 receptor blockers (ARB) combined or alone) was higher in the hyponatremic group than in the normonatremic group (p=0.04). Albumin (p=0.03) and hemoglobin (p=0.04) levels were significantly higher in normonatremic group than hyponatremic group. The biochemical properties of the groups are shown in Table 2.

Patients with MCI were older than those without (p=0.03), education level was lower (p=0.04) and diabetes frequency was increased in this group (p=0.02). Patients with MCI had lower GFR, hemoglobin, sodium, albumin values (p<0.05), higher urea, creatinine and proteinuria levels, and higher rates of diuretic (single and/or combined) use (p<0.05). Smoking and alcohol use were similar in patients with and without MCI (p>0.05). Patients with MCI had significantly higher DBP (92.5 ± 11.6 mmHg, 83.7 ± 10.9 mmHg, p=0.041), but there was no significant difference between the groups in SBP. Hemoglobin values of patients with MCI were lower than patients with normal cognitive function (respectively: 10.6 ± 2.1 g/dL, 11.7 ± 2.2 g/dL, p=0.03). Comparison of other clinical and laboratory parameters is shown in Table 2.

MoCA scores of hyponatremic and normonatremic patients were 19.6 ± 3.1, 23.4 ± 3.8, p=0.03, respectively. It was observed that hyponatremic patients had significant deterioration in language, attention, memory, verbal fluency, abstract thinking and executive functions compared to normonatremic patients. There was no significant difference between the groups in terms of orientation (p=0.13).

Correlation analyzes

A positive correlation was found between MoCA score and serum sodium levels (r=0.423, p=0.015). In addition, there was a significant negative correlation between MoCA score and age, creatinine, glucose, and DBP, and a positive significant correlation between hemoglobin level and eGFR (Table 3).

Multivariate logistic regression analyses

Multivariate logistic regression analysis was performed to evaluate the effects of age, diabetes, DBP, creatinine, eGFR, hemoglobin, albumin, and diuretic use on MCI (Table 4). Advanced age, diabetes, diuretic use, DBP and low sodium levels were determined as independent predictors for MCI.

Table 2. Comparison of demographic and biochemical characteristics of groups.

Parameter	Hyponatremia (n=33)	Normonatremia (n=112)	p	MCI (+) (n=78)	MCI (-) (n=67)	p
Age (years)	67.5 ± 12.8	54.3 ± 10.8	0.02	66.3±10.7	57.7±11.3	0.03
BMI (kg/m^2)	26.8 ± 3.1	27.5 ± 3.3	0.17	27.4 ± 4.1	26.9 ± 3.8	0.39
Female (n,%)	21, 53.1%	51, 55.4%	0.11	37, 47.4%	35, 52.2%	0.42
SBP (mmHg)	148.2±33.4	138.6±31.5	0.02	143.5±19.5	142.1±19.4	0.33
DBP (mmHg)	94.5±11.3	87.6±12.2	0.03	95.1±18.5	87.4±17.6	0.04
Glucose (mg/dL)	182.4±39.8	127.8±9.2	0.03	187.5±35.9	131.6±35.4	0.04
Urea (mg/dL)	68.8±7.1	67.8±6.8	0.24	67.7±7.4	67.1±8.2	0.49
Creatinine (mg/dL)	2.5±0.9	2.4±0.8	0.35	2.7±0.3	2.2±0.3	0.04
eGFR (ml/dk/1.73m^2)	29.8±4.5	30.2±4.8	0.38	26.8±4.4	33.2±4.9	0.04
Hemoglobin (g/dL)	10.8±1.9	11.7±2.1	0.04	10.6±1.6	11.5±2.2	0.03
Sodium (mmol/L)	130.6±15.2	138.8±16.4	0.04	131.6±24.6	137.2±23.9	0.02
Albumin (g/dL)	3.7±0.5	4.2±0.6	0.03	3.9±0.4	4.0±0.4	0.52
Calcium (mg/dL)	9.2±1.7	9.1±1.8	0.39	9.0±1.4	9.2±1.6	0.17
Phosphorus (mg/dL)	4.9±0.8	5.0±0.7	0.29	4.9±0.8	5.0±0.7	0.29
iPTH (pg/mL)	169.3±14.2	173.8±14.1	0.19	162.8±18.1	174.1±19.6	0.41
Bicarbonate (mEq/L)	21.6±3.7	20.9±3.8	0.37	20.2±3.4	22.3±3.6	0.07
C-reactive protein (mg/L)	6.1±0.7	6.3±0.8	0.22	6.2±0.5	6.2±0.6	0.61
Proteinuria (mg/day)	1567.2±154.7	1418.7±168.8	0.23	1767.2±154.7	1118.7±168.8	0.03
MoCA score	19.6±3.1 (13-24)	23.4±3.8 (19-28)	0.03	18.6±3.1 (13-22)	23.7±3.4 (19-28)	0.04

Abbreviations: eGFR: estimated glomerular filtration rate, BMI: Body mass index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MoCA: Montreal Cognitive Assesment, iPTH: intact parathyroid hormone

Table 3. The relationship between MoCA scores and clinical and laboratory parameters.

Parameter	r	p
Age (years)	-0.426	0.033
SBP (mmHg)	-0.128	0.093
DBP (mmHg)	-0.286	0.039
Glucose (mg/dL)	-0.294	0.043
Proteinuria (mg/g)	-0.329	0.069
Creatinine (mg/dL)	-0.327	0.041
C-reactive protein (mg/L)	-0.053	0.131
eGFR (ml/dk/1.73m^2)	0.392	0.037
Sodium (mmol/L)	0.423	0.015
Albumin (g/dL)	0.169	0.123
Hemoglobin (g/dL)	0.367	0.047

Abbreviations: eGFR: estimated glomerular filtration rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Table 4. Independent predictors of mild cognitive impairment in multivariate logistic regression analysis.

Parameter	OR	95% CI	p
Age (years)	1.452	1.293-2.035	0.037
Diabetes	2.028	1.137-4.762	0.016
Sodium (mmol/L)	1.439	1.064-2.139	0.011
Hemoglobin (g/dL)	1.523	1.284-2.414	0.026
eGFR (ml/dk/1.73m^2)	1.198	1.042-1.634	0.041
Diuretic use	1.052	1.004-1.187	0.208
DBP (mmHg)	1.336	1.127-1.571	0.028

Abbreviations: eGFR: estimated glomerular filtration rate, DBP: Diastolic Blood Pressure

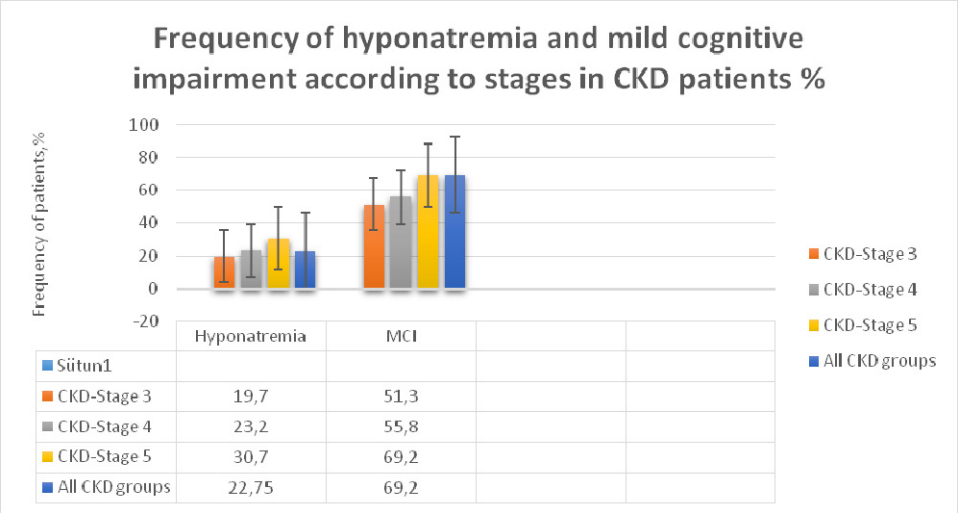

Fig 1. Frequency of hyponatremia and mild cognitive impairment according to stages in CKD patients.

DISCUSSION

In this study, the frequency of MCI was 53.7% and the frequency of hyponatremia was 22.7% in patients with CKD. The frequency of MCI in hyponatremic patients was significantly higher than in normonatremic patients. For MCI, advanced age, diabetes, DBP, low hemoglobin level, eGFR and diuretic use were determined as independent risk factors in multivariate logistic regression analysis, together with hyponatremia. The increased frequency of MCI in CKD patients may be due to the fact that MoCA is a reliable measure for detecting MCI. MoCA scale has 90% sensitivity in detecting MCI (17). A deficiency in at least one component of cognitive function tests that causes changes in the individual's activities of daily living supports the diagnosis of CI (5). The MoCA scale is considered superior to the Mini Mental State Examination, which is frequently used in screening CI (3). MoCA scores is superior to other cognitive tests in determining MCI and non-amnestic CI (18).

Psychiatric illnesses, are common among patients with advanced stage chronic kidney disease (19). CKD is characterized by progressive loss of cognitive functions. An increased risk of carotid atherosclerosis and stroke in patients with CKD is associated with cognitive dysfunction and dementia. Older adults with CKD have a 37% higher risk of developing dementia than older adults without CKD (5,20). MCI can be determined with the MoCA scale in patients with mild or no signs and symptoms of CI. The MoCA scale does not have an accepted cut-off value for all populations in detecting MCI. The cut-off value accepted for the diagnosis of

MCI in the original version of the MoCA scale is 26. Since the cut-off value used for MCI in this study was lower (<21 points), the frequency of MCI may have been high. The use of different MoCA scores for the diagnosis of MCI has been attributed to differences in cultural and educational factors between communities (7).

MCI is an intermediate form between normal cognitive functions and dementia and describes cognitive loss relative to those of similar age (8,18). Functional losses are not observed in individuals with MCI and they perform their daily activities without any problems. Since 6-40% of individuals with MCI progress to Alzheimer's type dementia annually, it is important to identify risky individuals (8). The cognitive domains most impaired in CKD patients are executive functions, attention, processing speed, and memory (21). While executive function and attention disorders are frequently observed in early-stage CKD patients, cognitive impairment is more severe in advanced-stage CKD patients and includes impairments in basic cognitive areas such as general cognitive abilities, executive function and episodic memory. Using different cognitive function tests in patients with CKD, albuminuria (22), N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) (4), uric acid (23), hemoglobin level (24), serum total testosterone (25), serum bicarbonate (26) levels and cognitive functions were evaluated and all parameters except serum bicarbonate level were found to be associated with cognitive functions.

Hyponatremia is seen with a frequency of 7% in healthy individuals, 11.6% over 75 years of age, and is the most common electrolyte disorder in patients admitted to the emergency services and hospitalized (10,27). Although mild hyponatremia is thought to be asymptomatic, in a study in which approximately 280.000 patients were evaluated, the frequency of hyponatremia was 15% during hospitalization and was associated with increased mortality rates regardless of the severity of hyponatremia (28). In our study, the frequency of hyponatremia in CKD patients was higher than in the general population. Hyponatremia is associated with CI in the general population, cirrhosis, brain tumor, and schizophrenia (11,13). In newly diagnosed hypertensive patient's, 24-h urinary sodium excretion was found to be associated with cognitive functions as assessed by a standart mini-mental test (29).

The etiology of CI seen in CKD is multifactorial, and various mechanisms have been proposed for the effect of hyponatremia. Although chronic hyponatremia is thought to be asymptomatic due to adaptation of the brain, it is associated with gait disturbances, fall risk, attention deficit, and CI (30). These symptoms are associated with decreased quality of life and increased morbidity and mortality rates. Chronic hyponatremia is associated with gait disturbances and cognitive disorders in rats with syndrome of inappropriate antidiuretic hormone secretion (30). In chronic hyponatremia, the brain is of normal size in volume due to adaptation, but the mitochondrial distribution of neurons is impaired and the adenosine triphosphate (ATP) content is decreased (30). Treatment of chronic hyponatremia with tolvaptan in the INSIGHT trial resulted in improvement in rapid motor movements (31). After 14 days of hyponatremia (chronic hyponatremia) in rats, brain glutamate content decreases by 38.6% (32). This indicates that synaptic excitatory neurotransmission are affected in chronic hyponatremia. In acute hyponatremia, the extracellular glutamate content of the brain increases (33). However, the contribution of hyponatremia alone to neurological symptoms and the underlying mechanisms are unclear.

From CKD stage-3, the frequency of CI increases by 11% for every 10 ml/min GFR decrease, and there is a non-linear relationship between GFR and cognitive disorders (34). In this study, the frequency of MCI was higher in CKD stage-5 patients than in stage 3-4 patients. As in the general population, advanced age, diabetes, and vascular diseases are risk factors associated with increased CI in CKD patients (21). Older CKD patients with CI have higher hospitalization, morbidity and mortality rates. It is important that these patients be evaluated with an appropriate test to identify CI. In this study, hospitalization and mortality rates with MCI were not evaluated, however, the frequency of MCI in patients over 65 was significantly higher than those under 65 years of age. In addition, diabetes was found to be an independent predictor for MCI in this study.

In patients with CKD, diabetes increases the risk of both amnestic and non-amnestic MCI by 21% (35). If the main function that is impaired in MCI is memory, it is classified as amnestic (precursor of Alzheimer's type dementia), and other cognitive functions are classified as non-amnestic MCI (precursor of vascular type dementia) (21). Patients with CKD often have non-amnestic CI (21). While executive function and attention are frequently affected in early-stage CKD patients, basic cognition areas such as general cognitive abilities, executive function and episodic memory are frequently affected in advanced-stage CKD patients (21).

Anemia adversely affects cognitive functions, and patients with CKD treated with erythropoietin show improvement in cognitive functions. In this study, low hemoglobin level was determined as an independent risk factor for MCI.

Some drugs used in patients with CKD are associated with CI. Hypertension is a risk factor for stroke, as well as contributing to the development of vascular cognitive impairment and dementia. Antihypertensive drugs may affect cognitive functions independently of their antihypertensive effects. While ACEi and ARB and calcium channel blockers affect cognitive functions positively, use of beta blockers and diuretics is associated with decreased cognitive functions (36). Although it has been stated that the cognitive functions of ACEi and ARB users are better in CKD patients, this effect may not be a group effect (37). In a study comparing lisinopril and candesartan, it was stated that neurocognitive functions were better in those using candesartan, and this effect was independent of its antihypertensive effect (37). Cognitive functions of patients using ACEi effective on the central nervous system are better than those without central effects. However, when ACEi and ARB group antihypertensives are used in combination with thiazide diuretics, hyponatremia caused by thiazide diuretics may mask the improvement in cognitive functions. In this study, 44.8% of the patients were using ACEi/ARB group antihypertensives. 50.7% of these patients were using without thiazide diuretic, 33.8% with thiazide diuretic and 15.5% combined with calcium channel blocker. The MoCA scores of the ACEi/ARB group without diuretics were higher, and this difference tended towards statistical significance (p=0.06).

Intact PTH levels in patients with MCI showed a high trend towards statistical significance (p=0.06). Low vitamin D levels are associated with CI, and vitamin D intake slows the rate of loss of verbal memory and produces a slower decline in visual memory/visual constructive abilities (38). However, vitamin D levels were not evaluated in this study.

This study has some limitations. The first is that it was single-centered, cross-sectional, and performed with a small number of patients. Due to its cross-sectional feature, it does not show the cause-effect relationship definitively. Second, the diagnosis of MCI is made by neurological examination, neuropsychiatric tests, and radiological imaging methods. In our study, cognitive functions were evaluated using the MoCA test. Many neurological diseases affecting cognitive functions such as silent infarction and white matter disease may not be detected without imaging studies. Third, the patients were not evaluated in terms of psychiatric diseases such as depression and anxiety disorder that caused CI. Another limitation is that patient’s daily salt consumption and sodium excretion in 24-h urine are not evaluated.

CONCLUSION

MCI is very common in patients with CKD and has a strong association with sodium levels. Advanced age, presence of diabetes, diuretic use, diastolic blood pressure, and low hemoglobin level are associated with MCI in patients with CKD. Evaluation of cognitive functions in CKD patients and correction of treatable risk factors may slow both CKD progression and progression to dementia. In CKD patients who use multiple drugs, the interaction with cognitive functions should also be considered in drug selection. Due to the increasing frequency of elderly CKD patients, it may be beneficial to include the evaluation of cognitive functions in the predialysis phase in nephrological follow-up.

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